Chapter 16

Analgesics, Antipyretic and Anti-inflammatory Agents

Analgesics

Analgesics are the drugs which relieve pain by acting on the central nervous system and they reduce pain without loss of consciousness. Analgesics can be divided into two main groups namely :

(A) **Narcotic analgesics.** These drugs produce depression of the central nervous system and are mainly of two types.

(*i*) Natural analgesics *e.g.* morphine, codeine etc.

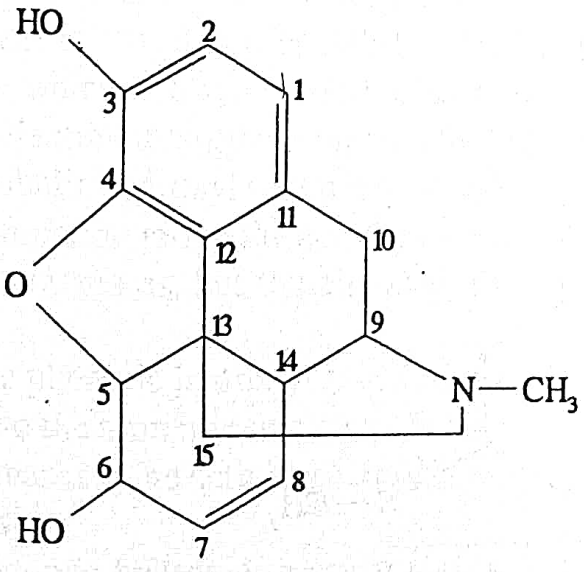
(*ii*) Synthetic analgesics *e.g.* pethidine, methadone etc.

(B) **Non-narcotic analgesics.** These drugs do not produce significant depression of the central nervous system. Unlike narcotic analgesics, the non-narcotic analgesics possess anti-inflammatory and antipyretic effect *e.g.* Salicylates and related compounds.

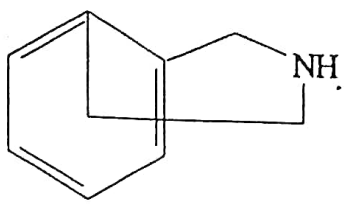
A. Narcotic analgesics

(Naturally Occurring) Morphine and its derivatives

Morphine. Morphine is an opium alkaloid obtained from unripe seed capsule of Papaver somniferum (poppy plant). Morphine is generally used as sulphate or hydrochloride. Morphine sulphate is a white odourless crystalline compound while its hydrochloride is obtained as a white powder), both are soluble in water. Morphine is a phenanthrene-isoquinoline alkaloid and has the following structure.



Morphine



Isoquinoline

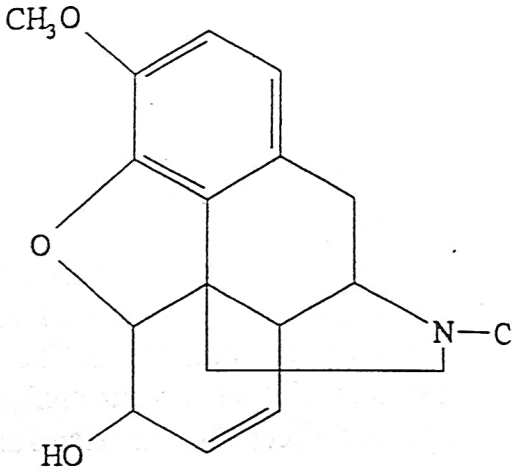
The solutions of morphine are sterilised at 98°C to 100°C for 30 minutes with a bactericide or by filtration.

Analgesic action of Morphine. Morphine is considered a powerful analgesic. It produces relief of pain in a dose which usually does not alter the other functions of central nervous system. The use of morphine does not lead to any abnormal behaviour or slurred speech. In large doses morphine can relieve all types of pain. Morphine reduces pain by increasing the threshold of pain which helps in producing an euphoria, *i.e.* a feeling of well being and it also modifies the emotional reaction to pain. Thus morphine does not remove pain completely, but in therapeutic doses, it helps the patient to tolerate the pain and the pain no longer remains as a source of concern. Morphine induces analgesia by acting on receptors situated both in the higher centers and the spinal cord.

Morphine produces a depression of respiration and it also produces miosis which results into excessive contraction of pupils and intake of morphine is characterised by pin-point pupils.

Uses. The main therapeutic use of morphine is as an analgesic for relieving the pain. Morphine is used to reduce pain in conditions such as acute myocardial infarction, fractures of bones, burns, pleurisy etc. Morphine can be administered intravenously for prompt relief of pain. It is also used to reduce post operative pain Morphine also shows sedative effect and is given to patient with internal bleeding etc. It also finds use in acute left ventricular failure. It is invaluable in the treatment of acute pulmonary-edema. Morphine is also used as premedication before surgery.

The major setback of morphine is that it is a drug of addiction due to its euphoriant effects. An overdose of morphine produces acute morphine poisoning. Other adverse side effects are dryness of mouth, mental clouding, dysphoria, vomiting, headache, fatigue, constipation etc. Other phenanthrene alkaloids of opium are codeine and buprenorphine.



Codeine

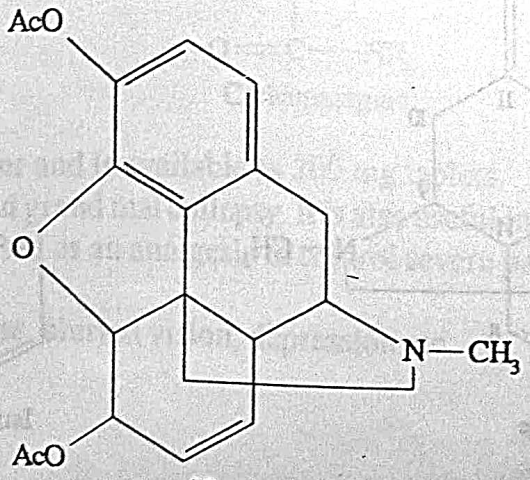
Codeine occurs as white crystalline powder and is sparingly soluble in water. It has some bit taste.

It is much less potent analgesic than morphine and unlike morphine it is much better absorbed wh administered orally.

Derivates of Natural Morphine

The important derivates of morphine are Heroin and Apomorphine, Dihydroxy morphine, Meth dihydromorphinone, Oxymorphone etc.

1. Heroin : It is a diacetyl derivative of morphine

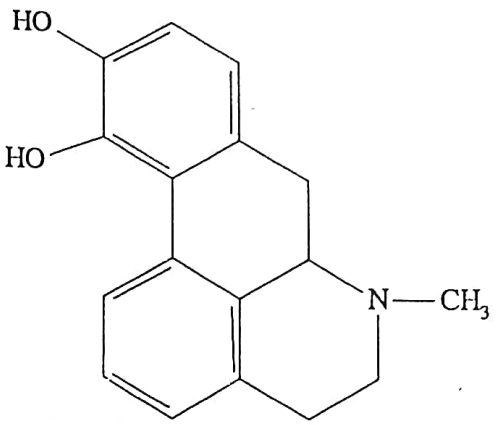


Heroin

It is more powerful analgesic than morphine and produces more euphoria. The tendency of addiction to this drug is much more than morphine and hence this drug is rarely used as analgesic.

2. Apomorphine : This drug is obtained by the acid-catalyzed re-arrangement of morphine.

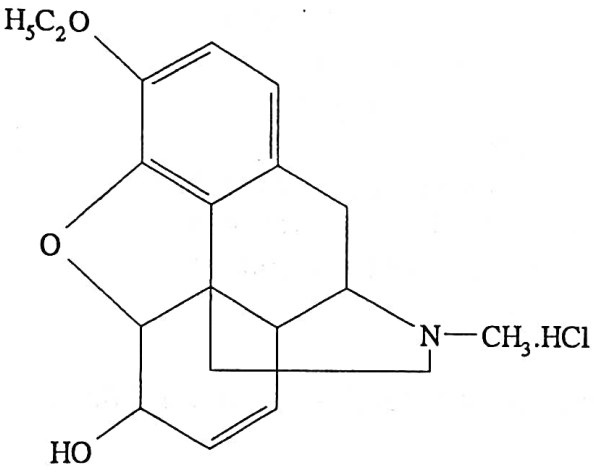
It is greyish white crystalline powder. It is sparingly soluble in water and alcohol. This drug is used as an emetic and is a stimulant of chemoreceptor triger zone. Apomorphine induces vomiting within a few minutes. It is administered parentally.



Apomorphine

Other important derivates of morphine are :

(1) Dihydroxy morphine,
(2) Oxymorphone,
(3) Methyl dihydromorphinones and
(4) Ethyl morphine hydrochloride.

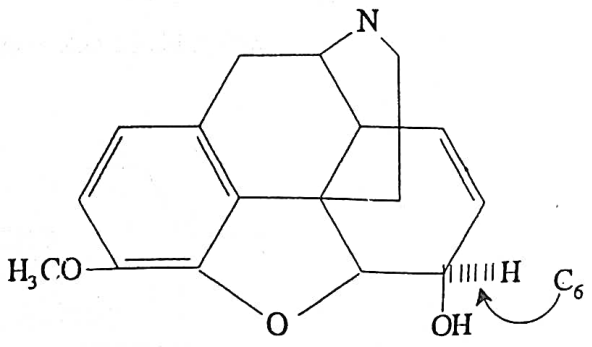


Ethylmorphine Hydrochloride

These drugs are effective analygesics and their duration of action lasts for 4-5 hours. Their toxicity is similar to that of morphine. Ethylmorphine hydrochloride is used in opthalmology in the form of drops and an ointment and as an anti-inflammatory agent.

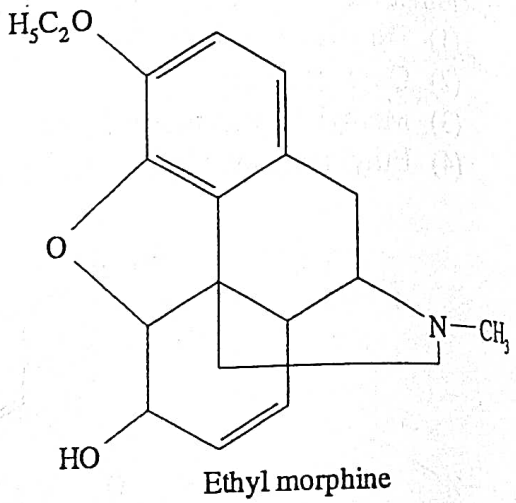
Structure activity relationship of Morphine

1. The physiological activity of morphine is attributed to the presence of phenanthrene skeleton.
2. The activity of morphine depends to a great extent on its stereochemical nature *e.g.* the natural morphine which is laevo rotatary shows analgesic activity whereas the synthetic morphine which is dextro-rotatory do not exhibit any activity.
3. If the alcoholic hydroxyl group is oxidised to a keto function group the activity of the morphine increases, but toxicity also increases.
4. When the phenolic hydroxyl (*i.e.* OH gp attached to the aromatic nucleus) of morphine is masked, the activity of morphine decreases.
5. If the alcoholic hydroxyl group at C-6 is shifted to C-8 position as in pseudocodeine the activity of morphine decreases.



α-isomorphine

6. Clevage of 4,5 oxygen bridge and substitution in the aromatic ring lowers the activity of morphine.
7. Activity of morphine enhances if there is saturation of 7.8 double bond.
8. Inversion of configuration of hydroxyl group at C-6 as in isomorphine increase the potency of morphine.
9. If both the hydroxyl groups, *i.e.* phenolic and alcoholic group of morphine are acetylated, it forms another compound known as Heroin, which is a powerful analgesic and is more addicting than morphine.
10. Substitution of alcoholic hydroxyl group by chlorine (chloromorphine) increases the potency of morphine by three times.
11. When hydroxyl group at C-6 is substituted by a hydrogen (dihydrodexoxy morphine D) the potency of morphine increases about ten times.
12. Substituting phenyethyl group in place of methyl group on nitrogen (N—CH3) yields a compound which is more active than morphine.
13. Generally introducing new substituents in the aromatic or alicyclic ring, decreases the potency of morphine, but there are some exceptions *e.g.* 5 methyl dihydro morphine known as metapan, is more potent then morphine.
14. Substituting the hydrogen aromatic hydroxyl group of an ethyl group. Morphine is converted to ethyl morphine which is as potent as morphine and is used as eye drops.



Ethyl morphine

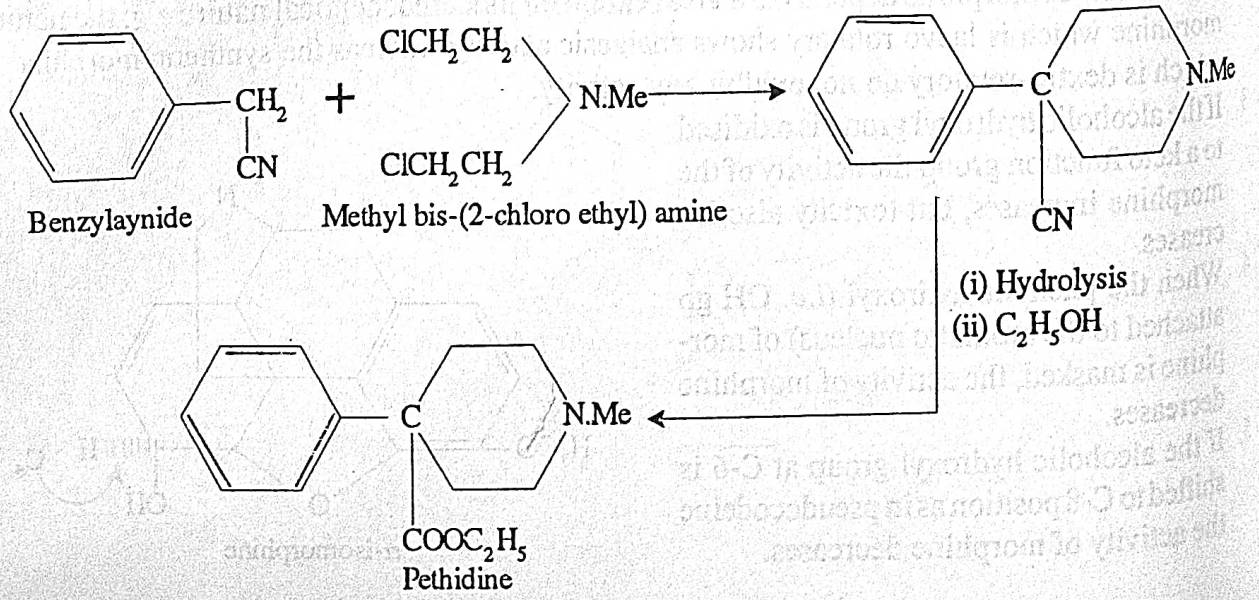
Synthetic analgesics

Some important synthetic morphine substitutes are as follows :

(*i*) Pethidine,
(*ii*) Methadone,
(*iii*) Morphinan and
(*iv*) Benzomorphan.

(*i*) **Pethidine (Meperidine, Demeral).** Pethidine is a white, crystalline substance with a bitter taste. It forms salts with acid. It is synthesised as follows:

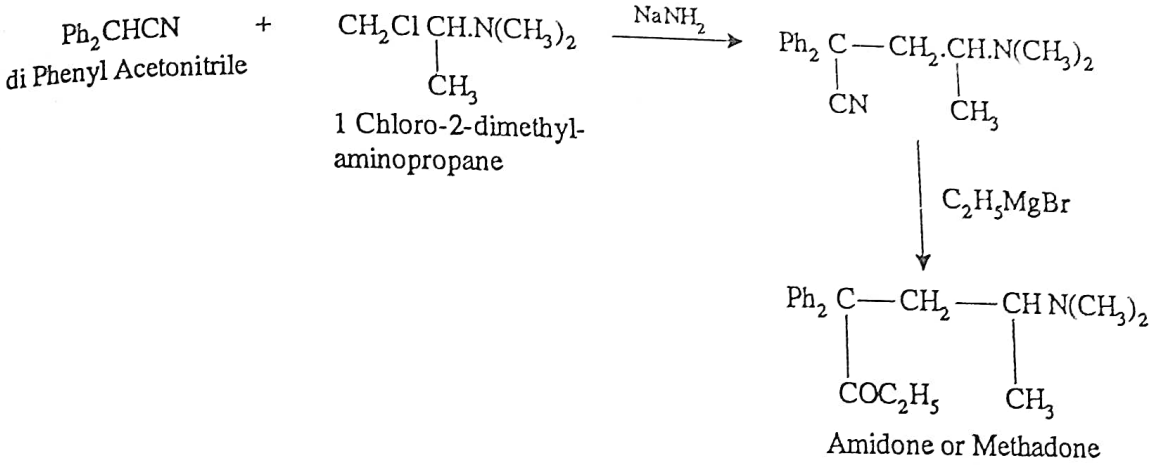
Its action is similar to that of morphine. Pethidine is a useful analgesic especially when short duration of action is required.



Benzylaynide
Methyl bis-(2-chloro ethyl) amine
Pethidine

Pethidine can be used in place of morphine as an analgesic in myocardial infarction, burns etc. It is a respiratory depressant like morphine. It is also used for the treatment of shock.

(*ii*) **Methadone.** (Amidone, Dolephine). It is a synthetic compound whose potency is slightly greater than morphine. It is synthesised as follows :

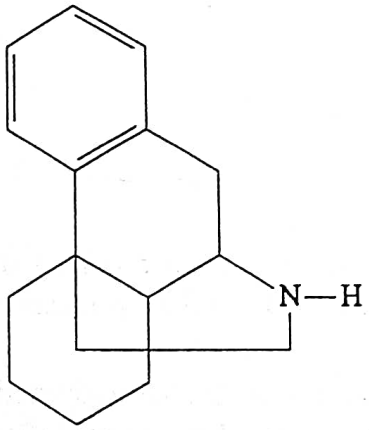


Amidone or Methadone

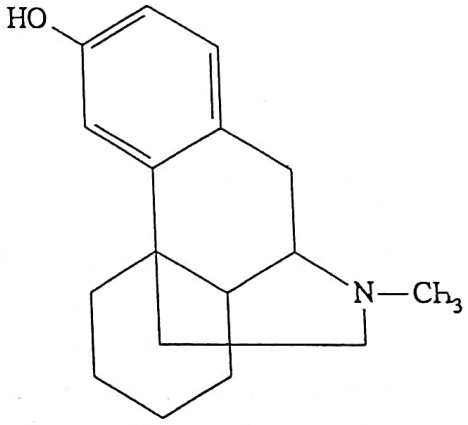
Methadone is available as Methadone hydrochloride tablet doses 5 to 10 mg. It is also available in ampoules in injection form. It is a racemic mixture and the *l*-isomer is more active than *d*-isomer.

It is used as a substitute for morphine and pethidine for relief of severe viceral pain. Methadone is also respiratory depressant.

(*iii*) **Morphinan.** This is also synthetic analgesic. It has the following structure.



Morphinan



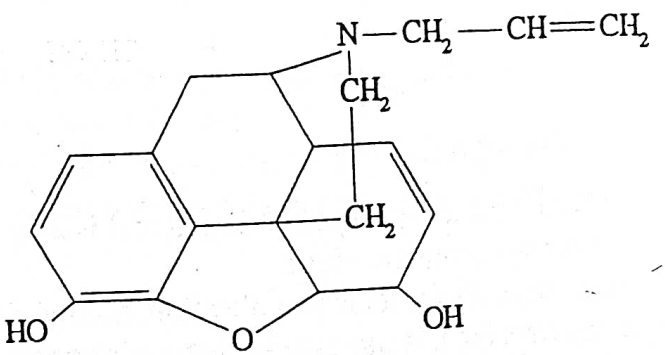
Levorphanol

An example of morphinan compounds is levorphanol. It is more potent analgesic than morphine and is well absorbed when administered orally.

(*iv*) **Benzomorphan compounds** *e.g.* Phenazocine, Pentazocine etc. It is a new synthetic agent and is much more potent than morphine. It is generally used intramuscularly in the dose of 2 to 3 mg.

Narcotic anatogonist

The drugs which are used as an antidote for the narcotic analgesics are called narcotic anatogonist. It antagonizes the effects of morphine, *e.g.* N-allyl morphine, Naloxone, Nalorphine, Levallorphan etc.



Nalorphine

B. Non-narcotic analgesics

These analgesics also possess antipyretic and anti-inflammatory property.

Antipyretic agents reduces the elevated body

temperature. The hypothalamus (situated at the base of the brain) plays an important role in regulating the body temperature. It regulates the body temperature by cutaneous vasodilation and by excessive sweating. In fever, the thermostatic mechanism is set at higher level and these antipyretic agents induce changes in the central nervous system in the region of the anterior of the hypothalamus and help to bring the thermostatic mechanism at the normal level.

Inflammation is a series of changes in tissues indicating their reaction to the tissues. The important aspects of inflammation are a superficial redness of the skin, edema and formation of granulation tissue. The anti-inflammatory agent reduces these conditions by controlling the cause of inflammation, *e.g.* Aspirin inhibits the synthesis of prostaglandins which are present in inflammatory exudate and cause edema, redness of skin, pain etc.

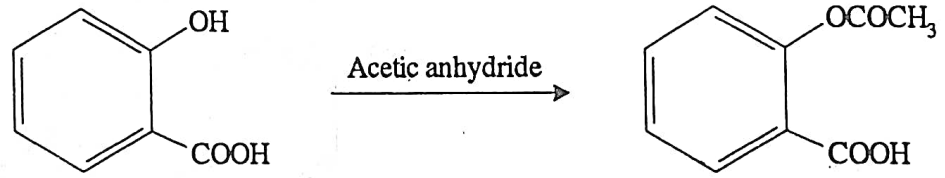
The non-narcotic analgesics are classified as

1. The Salicylic acid and its derivatives.
2. The Para-aminophenol derivatives.
3. The Pyrazole derivatives.
4. Indolyl and Aryl acetic acid derivatives.
5. Miscellaneous.

Salicylic Acid Derivatives

The derivative of Salicylic acid are well-known for their analgesic and antipyretic action. The most important drugs are aspirin (acetyl salicylic acid), sodium salicylate etc.

(*i*) **Aspirin (Acetyl Salicylic Acid).** It is obtained by the acetylation of Salicylic acid in the following manner :



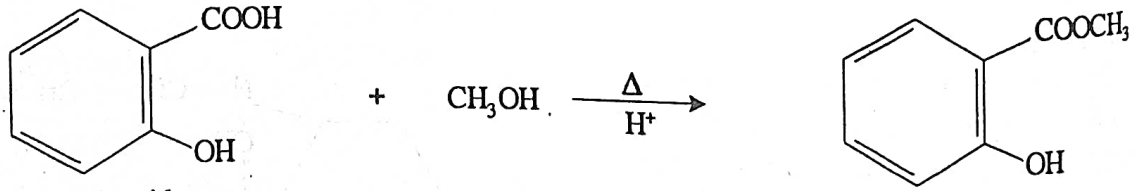
O-hydroxybenzoic acid or Salicylic acid

O-acetyl Salicyclic acid or Aspirin

Aspirin is white odourless, crystalline powder. It is sparingly soluble in water and has slight acid taste. In presence of moist air, it hydrolysis to Acetic acid (CH_3COOH) and Salicylic acid. It should be stored in airtight containers. It is stable in dry conditions. It melts at 135°.

Aspirin is used as an analgesic, only in cases in which pain is mild. It also has antipyretic action. It is used in headaches, colds, arthritis, toothache etc. Aspirin is also used as an anti-inflammatory agent. It helps in reducing edema, tissue swelling etc. It is also useful as antirheumatic drug and gives relief from signs and symptoms of inflammation. Aspirin has also shown beneficial effect in radiation diarrhoea.

(*ii*) **Methyl salicylate** (oil of winter green). Chemically it is O-hydroxy benzoate.



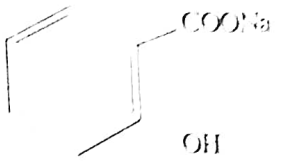
Salicylic acid

Methyl Salicylate

It is a colourless pale yellow liquid and is only slightly soluble in water. It has a sweet taste and characteristic aromatic odour.

It is used only for topical application. Methyl Salicylate ointment is made in white bees wax and hydrous wool fat. It is also used as a flavouring agent. It is applied as an analgesic in sciatica, rheumatic lumbago etc.

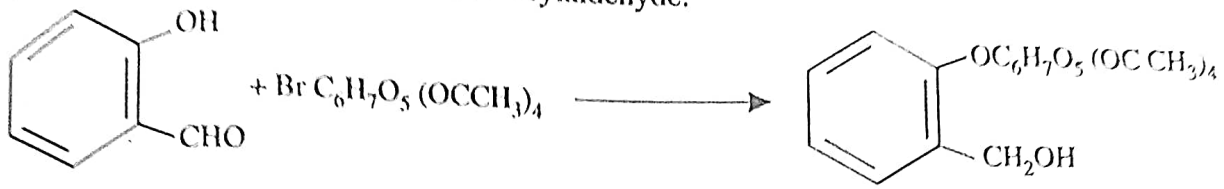
(*iii*) **Sodium Salicylate.** It occurs as colourless small crystals or as crystalline powder. It has characteristic unpleasant taste and is soluble in water.

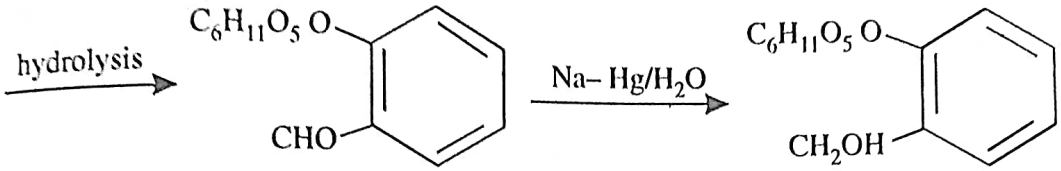


Sodium Salicylate

It is usually taken in a mixture form with alkali and is mainly used for integumental pain and acute rheumatic fever.

(*iv*) **Salicin.** It is obtained from bark of willows. It is also synthesised by the action of acetobromo-glucose and Salicylaldehyde.





Salicin

It is used in rheumatic pain and fever.

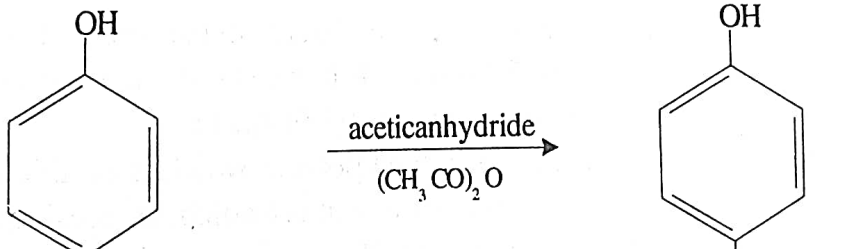
(*v*) **Diethylamine Salicylate.** It is a diethylamine salt of salicylic acid. It is a white crystalline substance and is soluble in water. It is used only topically and is available as creams and is used in rheumatic and muscular pain.

2. The para-aminophenol derivatives

These compounds have very pronounced analgesic and antipyretic effects. They are not useful anti-inflammatory drugs. The commonly used drugs are phenacetin (acetophenatidin) and para-acetamol (acetamainophen).

(*a*) **Para acetamol.** It is a white crystalline solid. It is 4-hydroxy Actanilide and is prepared as follows :

It is odourless and highly soluble in water. The total daily dose should not exceed 2.5% in adults.



P-aminophenol Paracetamol

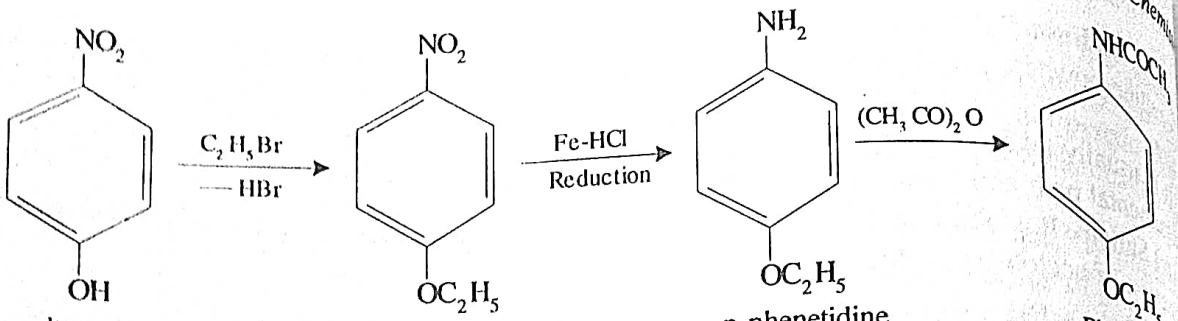
Paracetamol is more potent antipyretic than phenacetin. It is used for relief of pain and fever.

Adverse effect : Sweating, nausea, vomiting etc.

(*b*) **Phenacetin.** It is a white odourless, crystalline powder and is sparingly soluble in water. It has a slight bitter taste. It is prepared from *p*-nitrophenol as follows :

It is often used with aspirin for relief of integumental pain. It is more toxic than aspirin. Phenacetin is hydrolysed to paracetamol in vivo hence it is believed that phenacetin's, antipyretic-analgesic action is due to its hydrolysis to paracetamol.

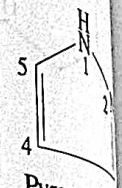
Adverse effect : More toxic than aspirin.



p-nitrophenol p-nitrophenetole p-phenetidine Phenacetin

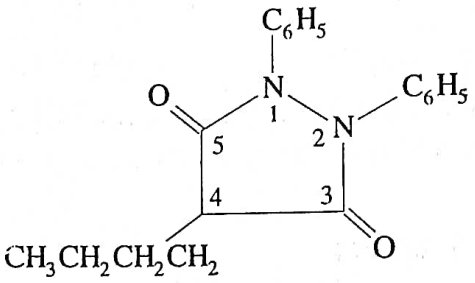
3. Pyrazole derivatives

These are pyrazole derivative, which is five-membered heterocycle compound having two adjacent nitrogens and two double bonds. If the ring is having one double bond, it is known as pyrazoline and if there are no double bonds it is known as pyrazolidine. There are many derivatives of these systems which are used as drug. Some important drugs are as follows :



Pyrazole Ri

(*i*) **Phenyl butazone.** It is white powder with slight bitter taste. It is sparingly soluble in w It has following structure.



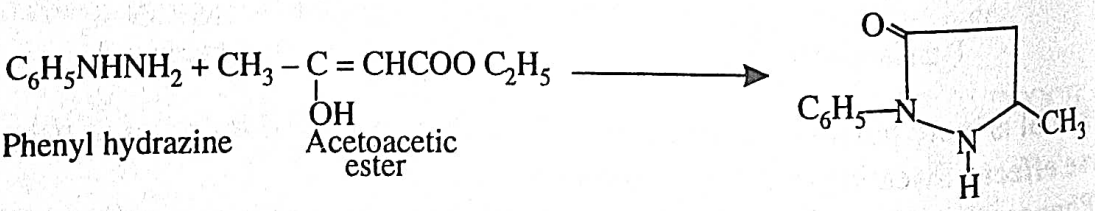
Phenyl Butazone

Chemically it is named as 4-butyl-1,2-di-phenyl pyrazolidine-3,5-dione. It is available as tab whereas its sodium derivative is available in ampoules containing 200 mg of phenyl butazone sodi per ml.

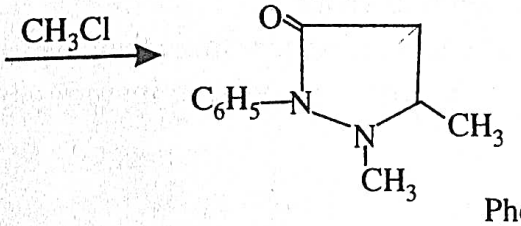
It is used for relieving pain in acute gout. It is also useful in the treatment of spondylitis and rheumatoid arthritis. It produces variety of side effects, hence it should not be employed routinel an analgesic or antipyretic.

(*ii*) **Oxyphenbutazone.** It is a degradative product of phenyl butazone. Chemically it is 4-bu 2-phenyl-1-hydroxy phenyl-pyrazolidine-3,5-dione. It has some therapeutic uses as that of phe butazone, but it causes less gastric irritation than phenyl butazone.

Phenazone (Antipyrine). It is a white crystalline powder which is soluble in water. Chemica it is named as 2,3-dimethyl-1 phenyl-3 pyrazolin-5-one. It is a potent analgesic and antipyretic. It a possesses anti-inflammatory activity. It is used in influenza fever. It is prepared as follows :

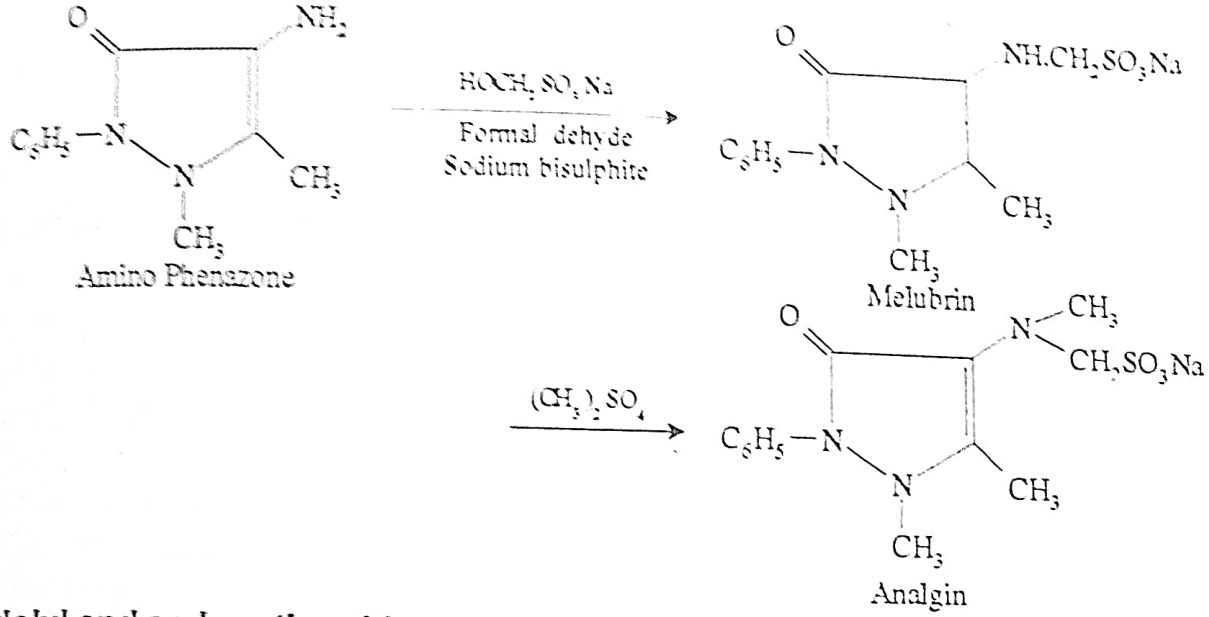


Phenyl hydrazine Acetoacetic ester



Phenazone

Analgin. It is a phenazone derivative, having $N(CH_3)CH_2SO_3Na$ substituent at position-4. It is a yellowish white powder and is soluble in water. It has slight bitter taste. It has potent analgesic and antipyretic action. It has toxic side effects hence it should not be used routinely to relieve pain and fever. It is prepared as follows :



Amino Phenazone

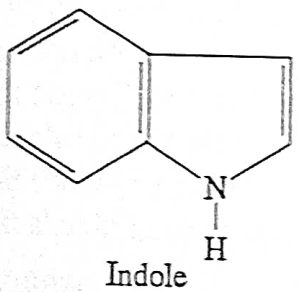
Melubrin

Analgin

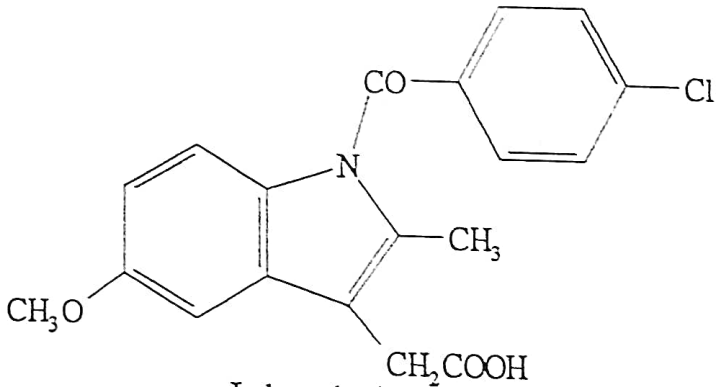
4. Indolyl and aryl acetic acid derivates

The important drugs of this group are as follows :

(*i*) **Indomethacin.** It is an indole acetic acid derivative. It has following structure.



Indole



Indomethacin

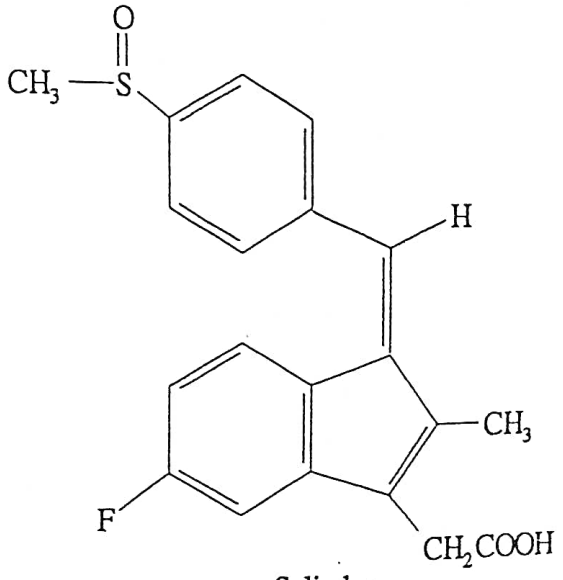
Chemically it is named as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3 indolylacetic acid. It is brownish yellow crystalline powder. It is insoluble in water, but it is soluble in organic solvents. It is available in 25 mg capsules.

This drug has inflammatory, analgesic and antipyretic actions. It is effective in rheumatic disorders. It is particularly useful in the treatment of gout.

It has some adverse side effects like nausea, vomiting, skin rashes, diarrhoea etc.

(*ii*) **Sulindac.** It is a fluorinated derivative of indomethacin. Chemically it is [5-fluoro-2 methyl-1 (4-methyl sulphinyl-benzylidene) inden-3 yl] acetic acid.

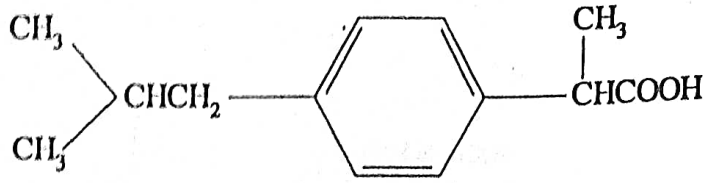
It occurs as yellow crystalline powder and is insoluble in water. It has longer duration of action than indomethacin. It used in the treatment of rheumatic and musculo-skeletal disorders.



Sulindac

5. Miscellaneous drugs

(*i*) **Ibuprofen (Brufen).** It is a synthetic compound and it is isobutylphenyl-propionic acid. Chemically it is named as 2-(4-isobutylphenyl) propionic acid.

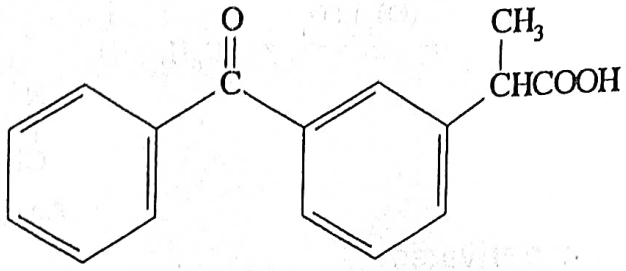


Ibuprofen

It is a white crystalline powder and is insoluble in water.

It has analgesic and weak anti-inflammatory action. It is used in rheumatoid disease. Its analgesic action is less than that of aspirin.

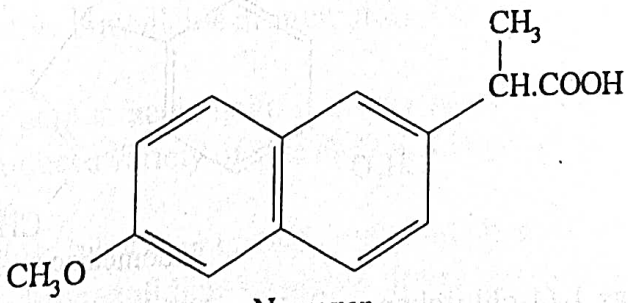
(*ii*) **Ketoprofen.** Chemically it is 2-(3-benzoyl phenyl) propionic acid.



Ketoprofen

It is white crystalline powder and is insoluble in water. It is more potent than Ibuprofen and is used in the dose of 150 mg. It has anti-inflammatory, analgesic, and antipyretic actions.

(*iii*) **Naproxen.** It is a propionic acid derivative and has methoxy-2-naphthyl group as substituent. It is a white crystalline powder and is insoluble in water. It is the dextrorotatory isomer.



Naproxen

It is used in the treatment of rheumatoid arthritis.

(*iv*) **Tromaril.** This is a anthranilic acid derivative. Chemically it is N-phenyl ethyl anthranilic acid. It has analgesic, antipyretic and anti-inflammatory properties. It is used orally in a dose of 1200-2400 mg per day.